TABLE 5. LEVEL OF HEPATITIS B VIRUS (HBV) DNA IN MEN WITH HEPATOCELLULAR CARCINOMA AND MATCHED CONTROLS WHO WERE POSITIVE FOR HEPATITIS B SURFACE ANTIGEN AND NEGATIVE FOR HEPATITIS B e ANTIGEN AT ENROLLMENT.

HBV DNA	MEN WITH HEPATOCELLULAR CARCINOMA (N=44)	MATCHED CONTROLS (N=86)	ADJUSTED ODDS RATIO (95% CI)*
	no. of men		
Undetectable (<2.5 pg/ml)†	27	74	1.0
2.5–13.0 pg/ml	7	7	2.3 (0.7–7.3)
>13.0 pg/ml	10	5	6.0 (1.7–21.4)‡

*The analysis was adjusted for age (as a continuous variable), the presence or absence of antibodies against hepatitis C virus, cigarette-smoking status, and use or nonuse of alcohol. P for trend = 0.003.

†This was the reference group.

‡P = 0.005.

mation of hepatocytes, as well as bind to the p53 tumor-suppressor gene and disrupt its functions.[25-30]

The presence of antibodies against HBeAg has been used as an important marker for the resolution of active HBV infection and for a sustained response to treatment with lamivudine alone or in combination with interferon alfa.[7] In the natural history of chronic hepatitis B, the spontaneous or interferon alfa–induced development of antibodies against HBeAg leads to improvement in the clinical outcome.[6,31] One study showed that patients who had a response to treatment with interferon alfa (i.e., clearance of HBeAg) were much less likely to have major liver complications during a five-year period of follow-up than were treated or untreated patients with persistent HBeAg.[31] A long-term controlled trial of treatment with interferon alfa showed that hepatocellular carcinoma developed more frequently in untreated patients than in treated patients and that it developed only in those with persistent HBeAg.[6] Our study showed that a negative test for HBeAg was associated with a low risk of hepatocellular carcinoma, suggesting that the earlier the development of antibodies against HBeAg occurs, the lower the risk of hepatocellular carcinoma.

We performed tests for HBsAg and HBeAg only at the time of enrollment. The effect of the appearance of antibodies against HBsAg and HBeAg on the development of hepatocellular carcinoma was not assessed. If the appearance of antibodies against HBeAg occurred after enrollment, the risk of hepatocellular carcinoma among men who were initially positive for HBeAg was underestimated. Tests for antibodies against HBeAg were not performed at the time of enrollment for men who were negative for HBeAg. However, we did perform tests for antibodies against HBeAg and for HBV DNA in frozen serum samples collected at the time of enrollment from the 44 men in whom hepatocellular carcinoma was subsequently diagnosed and the 86 matched controls, all of whom were initially positive for HBsAg and negative for HBeAg. In this nested case–control analysis, more than 90 percent of the men were positive for antibodies against HBeAg, and there was no significant difference in this respect between the men with hepatocellular carcinoma and the controls. However, positivity for HBV DNA was associated with a significantly increased risk of hepatocellular carcinoma.

HBV DNA is found in most patients who are positive for HBeAg, in a substantial proportion of those with antibodies against HBeAg (20 to 25 percent), and in some who are negative for HBeAg. Therefore, HBV DNA is the most important predictor of the development of hepatocellular carcinoma in HBsAg-positive Taiwanese men. However, the assay for HBV DNA is expensive and is performed only at specialized laboratories, whereas the assays for HBeAg, a surrogate marker of HBV DNA, and antibodies against HBeAg are inexpensive and are performed routinely. At present, a test for HBeAg may therefore be a more practical method for predicting the risk of hepatocellular carcinoma.

In conclusion, HBeAg, in addition to HBsAg, may be a useful marker of the risk of hepatocellular carcinoma. Persons considered to be at high risk because of positivity for HBeAg would be candidates for antiviral-drug treatment and close monitoring for the development of liver diseases associated with chronic HBV infection.

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APPENDIX

The following institutions and investigators, in addition to the authors, participated in the Taiwan Community-Based Cancer Screening Project Group: *National Taiwan University Hospital* — G.-T. Huang, H.-S. Lee, P.-M. Yang, C.-H. Chen; *Huhsi Health Center, Penghu County* — S.-C. Ho, T.-G. Lu; *Provincial Penghu Hospital* — W.-P. Wu, C.-T. Chen; *Sanchi Health Center, Taipei County* — C.-G. Lin; *Provincial Chutung Hospital* — C.-H. Lo; *Provincial Potzu Hospital* — Y.-Y. Kuo; *Kaohsu Health Center, Pingtung County* — C.-T. Lee, C.-C. Chen; and *Paihsa Health Center, Penghu County* — Y.-C. Ou, W.-C. How.

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Outline of Topic

Patient information: Hepatitis B

Anna SF Lok, MD

UpToDate performs a continuous review of over 375 journals and other resources. Updates are added as important new information is published. The literature review for version 15.3 is current through September 2007; this topic was last changed on February 12, 2007. The next version of UpToDate (16.1) will be released in March 2008.

INTRODUCTION — The liver is an organ that is located in the right upper abdomen, beneath the rib cage. It performs many functions that are essential to life including:

- Removal of toxins from the blood
- Metabolizing medications
- Producing blood proteins that are essential for normal blood clotting
- Manufacturing albumin, a protein required for maintaining normal fluid balance in the body
- Producing fluids and enzymes required for normal digestion

The term "hepatitis" is used to describe a common form of liver injury. Hepatitis simply means "inflammation of the liver" (the suffix "itis" means inflammation and "hepa" means liver). Hepatitis B is a specific type of hepatitis that is caused by a virus.

It is estimated that there are more than 3 00 million carriers of the hepatitis B virus in the world, with over 500,000 dyinig annually from HBV-related liver disease.

Fortunately, treatments for chronic hepatitis B are available, and many new treatments are in development. Vaccines have been developed that can prevent infection, and are now given routinely to newborns and children in the United States and in many other countries. Vaccination is highly recommended for adults who are at risk for acquiring the infection.

TRANSMISSION — The hepatitis B virus can be transmitted in a many ways. In the United States, the virus is most commonly transmitted by needle sharing during injection drug use or by unprotected sexual intercourse; in regions of the world where hepatitis B is prevalent, perinatal transmission (transmission from a mother to her baby) is the most common type of transmission.

Transmission by contaminated needles — Any activity that transfers blood or body fluids beneath the skin can transmit the hepatitis B virus. This includes tattooing, acupuncture, and ear piercing, if these procedures are performed with contaminated instruments. Needle sharing among injection drug users is another cause of transmission.

Sexual transmission — Transmission by unprotected sexual intercourse is the most common type of transmission of hepatitis B in developed countries. Sexual transmission accounts for about 30 percent of acute (new) cases of hepatitis B virus infection in the United States.

Perinatal transmission — Perinatal transmission refers to transmission from a mother to her baby near the time of birth. Transmission usually occurs during or shortly after delivery. There is no evidence that cesarean section prevents maternal-infant transmission, and breast-feeding does not appear to increase the risk of transmission. Infants of mothers known to have hepatitis B are usually given hepatitis B immunoglobulin (HBIG) and the hepatitis B vaccine as soon as possible after birth to reduce the chance that the infant will become infected. Babies who are infected around the time of birth have a 90 percent chance of developing chronic infection.

During pregnancy, all women should have a blood test for a marker of hepatitis B virus, called hepatitis B surface antigen (HBsAg). This marker is produced by HBV and indicates that the woman is currently or has previously been infected with HBV. If the mother's HBsAg test is positive, the infant should receive an injection of hepatitis B immunoglobulin (HBIG) soon after birth. HBIG is a passive immunization that temporarily helps to protect the infant from infection. The infant should also recieve the hepatitis B vaccine at birth, at 1 to 2 months, and at 6 months. The infant should have a blood test for hepatitis B infection at 9 to 18 months of age; if the test is negative, a fourth dose of the vaccine should be given at that time.

Transmission by close contact — Hepatitis B transmission can occur through close personal contact. Infection most likely occurs when body fluids containing the virus enter tiny breaks in the skin or the membranes of the eyes and mouth. This type of transmission often occurs between children. Because the virus can survive outside the body for long periods of time, transmission can also occur by sharing household items that carry the virus, including toys, toothbrushes, and razors.

Blood transfusion — Blood transfusion is now an uncommon route for the transmission of hepatitis B virus. Blood donors are carefully screened, and all donated blood is tested for markers of hepatitis infection. These procedures detect most contaminated units of blood, but a very small percentage of these units go undetected. As a result, people who require many blood transfusions during their lifetime (for conditions such as hemophilia or thalassemia) have an increased risk of hepatitis B. (See "Patient information: Blood donation and transfusion").

Transmission in the hospital setting — In the hospital setting, hepatitis B virus can be transmitted from patient to patient or from patient to health care provider through contaminated needles or instruments. Transmission from health care providers to patients is extremely rare. Measures to reduce this risk include using gloves, eye protection, a face mask, and hand washing, when appropriate.

Organ transplantation — Hepatitis B virus can be transmitted in donated livers and other organs. However, organ donors are routinely screened for hepatitis, which usually prevents this type of transmission.

SYMPTOMS — The symptoms of hepatitis B differ during acute (new) hepatitis and chronic (long-standing) hepatitis. Within these categories, the symptoms also vary widely from person to person. Most infected people, even those with progressive disease, have no specific symptoms for many years. However, the absence of symptoms does not necessarily mean that the infection is under control. All persons who have chronic infection with hepatitis B are at increased risk of developing complications that include the development of liver scarring (which in its advanced stage is termed cirrhosis) and liver cancer. (See "Patient information: Cirrhosis").

Acute hepatitis B — The symptoms of acute hepatitis B usually appear one- to four-months after infection. The first symptoms may be non-specific, including fever, skin rash, and joint pain and inflammation. Although many people have no symptoms at all, symptoms of acute hepatitis may include fatigue, loss of appetite, nausea, jaundice (yellowing of the skin), and pain in the upper right abdomen (where the liver is located). Acute hepatitis can be severe, with symptoms lasting for many weeks or months. Less commonly, acute hepatitis is life-threatening or "fulminant," in which the liver is so badly damaged that it can no longer function. The only treatment for fulminant hepatitis is liver transplantation.

The symptoms of acute hepatitis B usually resolve within three months as the body eliminates the virus or brings the virus under control. People with acute hepatitis rarely experience complications in other organs and tissues, and a very small percentage of people (0.1 to 0.5 percent) develop severe liver failure.

Most people with acute hepatitis B recover uneventfully. However, in about 5 percent of adults (1 in 20) the virus makes itself at home in the liver, where it continues to make copies of itself for many years. People who continue to harbor the virus are referred to as "carriers" while liver damage associated with longstanding infection is referred to as "chronic hepatitis."

Chronic hepatitis B — The symptoms of chronic hepatitis B can vary widely and can last for many years. Many people who carry the virus have no symptoms at all; other people have symptoms of ongoing liver inflammation, such as fatigue and loss of appetite. Some people with chronic hepatitis B experience sudden, temporary worsening of symptoms.

About 10 to 20 percent of people with chronic hepatitis B develop complications in other organs and tissues outside the liver; vascular inflammation and kidney disease are the two most common complications. People with chronic hepatitis B who develop cirrhosis or liver cancer may experience symptoms such as fatigue, weight loss, fluid accumulation in the abdomen and legs, bleeding, mental confusion, and abdominal pain.

Chronic hepatitis B develops more commonly in people who are infected with the virus at an early

age, such as at birth. Unfortunately, this is a common event in some parts of the world such as in southeast Asia, China, and sub-Saharan Africa, where as many as 1 in 10 people have chronic infection.

DIAGNOSIS — The diagnosis of hepatitis B is based upon a careful review of a person's medical history, the signs and symptoms noted during a physical examination, and the results of diagnostic tests.

Medical history — A detailed medical history may suggest the presence of hepatitis B and the likely route of infection. A healthcare provider will ask about risk factors for hepatitis B, including unprotected sexual intercourse and injection drug use, country of birth and any family history of hepatitis B. The clinician will also ask about any symptoms that have developed.

Physical examination — A physical examination is important to detect signs of acute hepatitis, including fever, yellowing of the eyes and skin (jaundice), a tender, slightly enlarged liver, and a skin rash. Most patients with chronic hepatitis B do not have any abnormal findings on examination. However, patients with advanced disease (such as those who have developed cirrhosis) can have a number of findings on physical examination as a result of the underlying liver problem. These include:

- Jaundice
- Confusion
- A distended, fluid-filled abdomen (ascites)
- An enlarged spleen
- Edema of the legs
- Enlarged breast tissue (in men)
- Redness of the palms (palmar erythema)
- Small, spider-like veins, usually on the chest and back (spider angiomas)
- Muscle wasting
- Atrophy of the testes
- Asterixis (spontaneous flapping of the hands when outstretched with the palms facing forward)

Liver tests — Liver tests are blood tests that provide information about the presence of liver damage and help determine the severity of damage and whether it has stopped or is ongoing.

- Alanine and aspartate aminotransferases — During acute hepatitis B, blood levels of two liver enzymes, alanine aminotransferase (ALT or SGPT) and aspartate aminotransferase (AST or SGOT), are usually elevated. High levels of these enzymes signal ongoing liver inflammation. In most people with acute hepatitis, levels return to normal within one to four months. The persistence of high ALT levels after six months suggests that a person is developing chronic hepatitis. Liver enzyme levels may be more than 1000 IU/L during acute hepatitis but may vary from normal (less than 40 IU/L) to a few hundred in patients with chronic infection. Liver enzyme levels may fluctuate during the course of chronic infection.

- Bilirubin — High blood levels of bilirubin (a substance produced mostly from red blood cells and metabolized by the liver) often signal more severe liver damage. High bilirubin levels give rise to jaundice, which is yellowing of the skin and eyes and darkening of the urine.

- Albumin — Low blood levels of albumin, a protein synthesized by the liver, often signal chronic liver damage.

- Prothrombin time — An abnormally long prothrombin time (a measure of the time required for blood clotting) or high international normalized ratio (INR, another way of reporting prothrombin time) suggests more severe liver damage. The results of a prothrombin time are the best predictor of outcome in acute hepatitis B.

Hepatitis markers — Levels of several hepatitis markers found in the blood can confirm hepatitis B infection and differentiate acute from chronic infection. These markers include substances produced by the hepatitis B virus (called antigens) and substances produced by the immune system to control and eliminate the virus (called antibodies).

The diagnosis of acute hepatitis B is based upon the presence of the hepatitis B surface antigen (HBsAg) and hepatitis B core IgM antibody. The diagnosis of chronic hepatitis B is based on the

presence of the HBsAg marker for at least six months; hepatitis B core IgM antibody is usually negative.

- Hepatitis B surface antigen — In acute hepatitis, HBsAg can be detected soon after infection; falling levels of this marker and the appearance of hepatitis B surface antibodies (HBsAb or anti-HBs) signal recovery. In chronic hepatitis, HBsAg can be detected for many years, and HBsAb may never appear.

- Hepatitis B e antigen — Hepatitis B e antigen (HBeAg) is present when the hepatitis B virus is actively multiplying. In acute hepatitis, HBeAg can be detected soon after infection; falling levels of this marker and the appearance of hepatitis B e antibodies (HBeAb or anti-HBe) signal recovery. In most patients with chronic hepatitis, HBeAg can be detected for many years. With time, the immune system may suppress the virus to such low levels that HBeAg is no longer detected and HBeAb is present. Loss of HBeAg and appearance of HBeAb (also called HBeAg seroconversion) is usually an indication that the virus is suppressed and the liver disease becomes inactive. However, some HBV mutants that cannot make HBeAg have been described (precore mutants). In this case, patients may be HBeAg negative but still have high levels of virus and active liver disease.

- Hepatitis B virus DNA — Detection of hepatitis B virus DNA in a blood sample signals that the virus is actively multiplying. In acute hepatitis, HBV DNA can be detected soon after infection; falling levels of HBV DNA signal recovery, and levels usually become undetectable over time. In chronic hepatitis, levels of HBV DNA often remain high for many years and then decrease as the immune system gains control over the virus. In some patients, HBV DNA levels fluctuate due to alterations in balance between the immune system and the virus.

- Antibodies to Hepatitis B core antigen — In acute hepatitis, a specific class of antibodies (IgM) directed against the hepatitis B core antigen (anti-HBc) appears early in infection. There are two classes of this antibody (core IgG and core IgM). The IgM class appears first during the acute phase of hepatitis and then gradually switches to the IgG type.

Antibodies to Hepatitis B surface antibody (anti-HBs) is a marker of immunity or protection. Persons who develop immunity to hepatitis B after vaccination have anti-HBs only while those who develop immunity after recovery from acute hepatitis B have anti-HBs and the IgG type of anti-HBc.

Liver biopsy — During a liver biopsy, a small sample of liver tissue is collected for microscopic examination. A liver biopsy is not routinely needed to diagnose hepatitis B. Liver biopsy is used for monitoring the progression of liver damage in people with chronic hepatitis, helping to decide if treatment is needed, and for detecting cirrhosis or liver cancer. (See "Patient information: Liver biopsy").

TREATMENT — There is no specific treatment for acute hepatitis B; in 95 percent of adults, the immune system controls the infection and eliminates the virus within about six months. Antiviral treatment may be considered in the rare patient with very severe acute or prolonged acute hepatitis B. In people who develop chronic hepatitis, the goals of treatment are to stop the virus from multiplying to reduce or reverse liver damage.

General measures — All persons with chronic hepatitis B should be vaccinated against hepatitis A unless they are known to be immune. Pneumococcal vaccine is recommended every five years, and influenza vaccination is recommended once per year. Patients with liver disease should also receive standard immunizations, including diphtheria and tetanus booster immunizations every ten years. (See "Patient information: Adult immunizations").

Regular screening for liver cancer is also recommended, particularly for older individuals, those with cirrhosis, and patients with family history of liver cancer. In general, this entails an annual or biannual ultrasound examination and blood test for the alpha fetoprotein level (a protein produced by some liver tumors, which is detectable in blood). The best approach to screening for liver cancer has not been determined.

Antiviral therapy — Six drugs that can slow or stop multiplication of the hepatitis B virus are available: lamivudine, adefovir, entecavir, telbivudine, interferon-alpha, and pegylated interferon-alpha. Not all hepatitis B patients will benefit from these treatments. The physician and the patient should discuss treatment options after a careful assessment of the individual's conditions. Regular monitoring is needed during treatment to monitor for response, side effects and drug resistance, and for relapse after treatment is stopped. Some patients benefit from treatment when hepatitis becomes more active, which requires that the patient is monitored periodically.

Lamivudine — Lamivudine (Epivir-HBV®) is effective in decreasing virus activity and ongoing liver inflammation. It is safe in patients with liver failure and long-term treatment can decrease the risk of liver failure and liver cancer.

Lamivudine is taken by mouth, usually at a dosage of 100 mg/day. The major problem with lamivudine is that a resistant form of hepatitis B virus (referred to as a YMDD mutant) frequently develops in people who take lamivudine for long-term treatment. Appearance of the mutant virus may be accompanied by a marked increase in virus level and a flare of hepatitis, and in rare instances, liver failure. Lamivudine is used less commonly in patients who require long-term treatment because new drugs are available that are less likely to cause resistance.

Adefovir — Adefovir (Hepsera®) is an alternative initial choice for people who have detectable virus activity and ongoing liver inflammation. An advantage of adefovir compared to lamivudine is that resistance to the drug occurs at much lower rates. In addition, adefovir can suppress lamivudine- resistant hepatitis B mutants. Adefovir has been associated with kidney problems when used in high doses or for long durations, so kidney function needs to be monitored before and during treatment. Adefovir acts slowly in some patients, additional treatment may be needed in those with little or no decrease in HBV DNA levels after six months of adefovir.

Adefovir is taken orally, at a dosage of 10 mg/day, for at least one year. Most patients will need long-term treatment to maintain control of the hepatitis B virus.

Entecavir — Entecavir (Baraclude®) is a relatively new drug, so its benefits and safety are still being determined. An advantage compared with lamivudine, telbivudine, and adefovir is its greater potency against the hepatitis B virus. To date, resistance seems to be rare. A disadvantage is its relatively higher cost, relative to the other oral HBV drugs. It is also effective against lamivudine-resistant hepatitis B, although it is not as potent as adefovir for this condition.

Entecavir is taken orally, at a dosage of 0.5 mg daily for patients who have no prior treatment and 1.0 mg daily for patients who have resistance to lamivudine, for at least one year. Most patients will need long-term treatment to maintain control of the hepatitis B virus.

Interferon-alpha — Interferon-alpha is an appropriate treatment for people with chronic hepatitis B infection who have detectable virus activity, ongoing liver inflammation,and no cirrhosis. Both conventional interferon (which has to be given daily or three times a week) and pegylated interferon are approved in the United States. Interferon-alpha is not appropriate for people with cirrhosis who have liver failure or for people who have a recurrence of hepatitis after liver transplantation.

Interferon is given for a finite duration (4 to 12 months) in contrast to the oral HBV drugs which are given for many years until a desired response is achieved. Drug resistant mutations to interferon have not been reported.

Interferon-alpha must be taken by injection. The drug triggers a flare of hepatitis in 30 to 50 percent of people who are HBeAg positive, although flares are uncommon in those who are HBeAg negative. These flares usually do not cause symptoms but in rare cases, usually in patients with cirrhosis, can be fatal. The disadvantage of interferon-alpha is that it can cause many side effects. Interferon-alpha may be considered in young patients who do not have advanced liver disease and do not wish to be on long-term treatment.

Telbivudine — Telbivudine (Tyzeka®) is similar (but slightly more potent) than lamivudine. Unfortunately, it is associated with a high rate of resistance, similar to lamivudine.

Liver transplantation — Liver transplantation may be the only option for those who have developed advanced cirrhosis. The transplantation process is elaborate, involving an extensive screening process to ensure that a person is a good candidate. Thus, not all patients with cirrhosis are eligible, and only those with the most advanced cirrhosis and otherwise good medical and social conditions will be put on the transplant waiting list.

PROGNOSIS — As discussed above, the clinical course of hepatitis B can vary widely. Certain factors help predict prognosis.

Likelihood of developing chronic infection — The likelihood of acute hepatitis progressing to chronic hepatitis largely depends on a person's age at the time of infection. Chronic infection develops in about 90 percent of children who are infected at birth, in 20 to 50 percent of children who are infected between the ages of 1 and 5 years, and in less than 5 percent of people infected during adulthood.

Factors that influence prognosis — Several factors affect the prognosis of chronic hepatitis. Prognosis is largely influenced by the extent of viral multiplication and the immune system's ability to control the infection. Other factors that appear to worsen the course of hepatitis include

male gender, habitual alcohol consumption, and coinfection with other hepatitis viruses.

TIPS TO MAINTAIN LIVER HEALTH — As discussed above, the majority of people with acute hepatitis B spontaneously clear the infection. Those who develop chronic infection should be evaluated by a physician with expertise in liver disease (usually a gastroenterologist or hepatologist) who can discuss treatment options. In addition to the routine vaccinations discussed above and the need to screen for liver cancer, a number of other issues may be discussed:

Diet — No specific diet has been shown to improve the outcome in patients with hepatitis B. The best advice is to eat a normal healthy and balanced diet.

Alcohol — Alcohol should be avoided since it can worsen liver damage. All types of alcoholic beverages can be harmful to the liver. Patients with liver disease may worsen even with small amounts of alcohol.

Exercise — Exercise is good for overall health and is encouraged, but it has no effect on the virus.

Prescription and nonprescription drugs — Many medications are broken down by the liver. Thus, it is always best to check with a healthcare provider or pharmacist before starting a new medication. As a general rule, unless the liver is already scarred, most drugs are safe for people with hepatitis B. An important possible exception is acetaminophen (Tylenol®); the maximum recommended dose in those with liver disease should be no more than 2 grams (650 milligrams per dose) in 24 hours.

Herbal medications — Although many claims about herbal medications have been made (particularly on the internet), no herbal treatment has been proven to improve outcomes in patients with hepatitis B, and some can cause serious liver toxicity.

Support — Sharing concerns with others infected with hepatitis B can provide support. A number of organizations are available around the world. (See "Where to get more information" below).

IMPLICATIONS FOR THE FAMILY — Acute and chronic hepatitis B are contagious. Thus, people with hepatitis B should discuss measures to reduce the risk of infecting others. This usually involves minimizing blood and bodily fluid exposure, testing immediate family and household members, and vaccinating those at risk for acquiring the infection. (See "Patient information: Adult immunizations").

WHERE TO GET MORE INFORMATION — Your healthcare provider is the best source of information for questions and concerns related to your medical problem. Because no two patients are exactly alike and recommendations can vary from one person to another, it is important to seek guidance from a provider who is familiar with your individual situation.

This discussion will be updated as needed every four months on our web site (http://www.patients.uptodate.com/). Additional topics as well as selected discussions written for healthcare professionals are also available for those who would like more detailed information. Some of the most pertinent include:

Professional Level Information:
Clinical manifestations and natural history of hepatitis B virus infection
Epidemiology; transmission and prevention of hepatitis B virus infection
Overview of the management of chronic hepatitis B and case examples
Serologic diagnosis of hepatitis B virus infection
Standard and pegylated interferon for chronic hepatitis B virus infection
Treatment and prevention of hepatitis B in the HIV-infected patient
Adefovir dipivoxil in the treatment of chronic hepatitis B virus infection
Characteristics of the hepatitis B virus and pathogenesis of infection
Clinical significance and molecular characteristics of common hepatitis B virus variants
Clinical significance of hepatitis B virus genotypes
Combination therapy for chronic hepatitis B virus infection
Hepatitis B virus vaccination
Immunizations for patients with chronic liver disease
Lamivudine monotherapy for chronic hepatitis B virus infection
Newer treatments of chronic hepatitis B virus infection
Telbivudine in the treatment of chronic hepatitis B virus infection

A number of web sites have information about medical problems and treatments, although it can be difficult to know which sites are reputable. Information provided by the National Institutes of Health, national medical societies and some other well-established organizations are often reliable sources of information, although the frequency with which they are updated is variable.

- National Library of Medicine

(www.nlm.nih.gov/medlineplus/healthtopics.html)

- Centers for Disease Control

(www.cdc.gov/ncidod/diseases/hepatitis/index.htm)

- National Institute of Diabetes and Digestive and Kidney Diseases

(http://www.niddk.nih.gov/)

- National Institute of Allergy and Infectious Diseases

(www.niaid.nih.gov/)

- National Foundation for Infectious Diseases

(http://www.nfid.org/)

- American Association for Study of Liver Diseases

(http://www.aasld.org/)

- American Gastroenterological Association

(http://www.gastro.org/)

- American Liver Foundation

(http://www.liverfoundation.org/)

- The Hepatitis B Foundation

(http://www.hepb.org/)

[1-9]

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BRIEF REPORT

Hepatitis B Vaccination and Hepatocellular Carcinoma Rates in Boys and Girls

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Context Hepatocellular carcinoma (HCC) has a male predominance and is closely related to hepatitis B virus (HBV) infection. Hepatitis B virus vaccination was launched in 1984 in Taiwan for neonates of mothers carrying hepatitis B e antigen, resulting in a decreased incidence of HCC in children. The effect on boys vs girls is not known.

Objective To evaluate the association between a HBV vaccination program with incidence of childhood HCC by sex.

Design and Setting Analysis of data collected from Taiwan's National Cancer Registry System and the Taiwan Childhood Hepatoma Study Group between 1981 and 1996.

Participants Children aged 6 to 14 years who were diagnosed as having HCC (201 boys and 70 girls).

Main Outcome Measure Incidence of HCC in boys and girls before and after implementation of the vaccination program.

Results The boy-girl incidence ratio decreased steadily from 4.5 in 1981-1984 (before the program's introduction) to 1.9 in 1990-1996 (6-12 years after the vaccination program was launched). The incidence of HCC in boys born after 1984 was significantly reduced in comparison with those born before 1978 (relative risk [RR], 0.72; $P=.002$). No significant decrease in HCC incidence was observed in girls born in the same periods (RR, 0.77; $P=.20$). The incidence of HCC in boys remained stable with increasing age, while an increase of HCC incidence with age in girls was observed. These age and sex effects remained the same regardless of birth before or after the vaccination program.

Conclusion Our results suggest that boys may benefit more from HBV vaccination than girls in the prevention of HCC.

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HEPATOCELLULAR CARCINOMA (HCC) occurs mainly in adults 40 to 60 years of age.[1] However, in areas hyperendemic for hepatitis B virus (HBV) infection, HCC may develop in children.[2] We have found a nearly 100% hepatitis B surface antigen seropositivity rate in Taiwanese children with HCC, indicating an intimate relationship between HBV and childhood HCC.[2] In 1984, a hepatitis B vaccination program was launched and has effectively reduced the prevalence of HBV infection, chronic HBV infection rate,[3] and incidence of HCC in children in Taiwan.[4]

A male predominance of HCC has long been observed.[5,6] The mechanism is unknown, but a tumorigenic effect of androgens has been suggested.[7] We found a male-female ratio of 3-4:1 in children with HCC,[8] which is similar to that in adults. Since the influence of hormones in children is much less than that in adults, investigating HCC in children may facilitate understanding of the mechanism of HCC. We therefore studied children with HCC by sex before and after the implementation of the HBV vaccination program.

METHODS

Subjects

A vaccination program was implemented in Taiwan in July 1984.[9] Hepatitis B immunoglobulin was given to neonates of highly infectious mothers carrying hepatitis B e antigen. All infants received 3 or 4 doses of HBV vaccine.

According to our previous observation, HCC in children was diagnosed mainly in those older than 6 years,[2] while hepatoblastoma was diagnosed in younger children.[10] In this study, we included children 6 to 14 years of age with liver cancer to preclude the inclusion of hepatoblastoma.

Two independent childhood hepatoma registry systems were used in this study to ensure accuracy. Data from the following 2 systems, including the name, identification number, birth date, sex,

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Members of the study group are listed at the end of this article.

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Table 1. Incidence of Hepatocellular Carcinoma in Boys and Girls Aged 6 to 14 Years in Taiwan, 1981-1996

	Boys			Girls				
Year of Diagnosis*	No. of Cases	Population	Incidence†	No. of Cases	Population	Incidence†	Total Incidence	Male-Female Ratio
1981-1984	56	5 182 103	1.08	12	4 897 529	0.24	0.67	4.5
1984-1990	94	10 753 818	0.87	33	10 143 281	0.32	0.61	2.7
1990-1996	51	10 396 566	0.49	25	9 769 501	0.26	0.38	1.9

*1981-1984, July 1981 to June 1984; 1984-1990, July 1984 to June 1990; and 1990-1996, July 1990 to June 1996.
†Number per 100 000 population.

address, etc, were checked and merged, and any repetition was deleted. The case information was confirmed by the reporting hospitals. The capture-recapture method was used to estimate the total number of cases of childhood HCC (Epi Info, version 6.04; Centers for Disease Control and Prevention and the World Health Organization). The number of cases identified by systems 1 and 2 was estimated to be 86% (95% confidence interval [CI], 80%-92%) of the actual total number of children with HCC.

System 1: National Cancer Registry System

Cases of hepatoma diagnosed between July 1981 and June 1996 were analyzed from the data bank of the National Cancer Registry System at the National Department of Health. This registry was established in 1979. Cases are reported by the department of medical records in each of the 167 hospitals with more than 50 beds in Taiwan.

System 2: Multicenter Childhood Hepatoma Study Group

To ensure the accuracy of the data from the National Cancer Registry, we formed a multicenter Childhood Hepatoma Study Group to register children with hepatoma during the same study period. Pediatric gastroenterologists or oncologists from 17 major hospitals, including all 12 tertiary referral centers in Taiwan, participated.

Statistical Analysis

The study population was stratified both by age at diagnosis and the year of birth. Children with HCC who were older than 6 years on July 1, 1984, when the HBV vaccination program was launched, were born before July 1978. Children born before 1978 and after 1984 were the respective cohorts without and with the effect of HBV vaccination. Children born between 1978 and 1984 were born during the transition to full implementation of the HBV vaccination program. They might have received HBV vaccination beyond infancy.

Age-specific and birth-year–specific incidences of HCC were calculated for boys and girls. Relative incidences of HCC among children divided into groups by age, birth cohort, and sex were analyzed using Poisson regression.[11] The modification of age effect on HCC incidence by sex was statistically tested by cross production of age and sex variables (the interaction term) and expressed in separate models when the age trends were significantly different between female and male.

Table 2. Effect of Birth Year on the Development of Childhood Hepatocellular Carcinoma by Sex*

	Boys		Girls	
Birth Year	RR (95% CI)	*P* Value	RR (95% CI)	*P* Value
1966-1977	1.00 (Referent)		1.00 (Referent)	
1978-1983	0.83 (0.71-0.96)	.02	1.02 (0.79-1.30)	.90
1984-1989	0.72 (0.59-0.89)	.002	0.77 (0.52-1.15)	.20

*RR indicates relative risk; CI, confidence interval.

RESULTS

A consistent predominance of HCC in boys was found throughout the observation period. The incidence of childhood HCC declined gradually in boys during 1981-1996, while the incidence in girls remained stable (TABLE 1). Although the trend of the predominance in boys remained, the boy/girl ratio of the incidence of HCC declined gradually with time from 4.5 for years of diagnosis 1981-1984 to 1.9 for years of diagnosis 1990-1996.

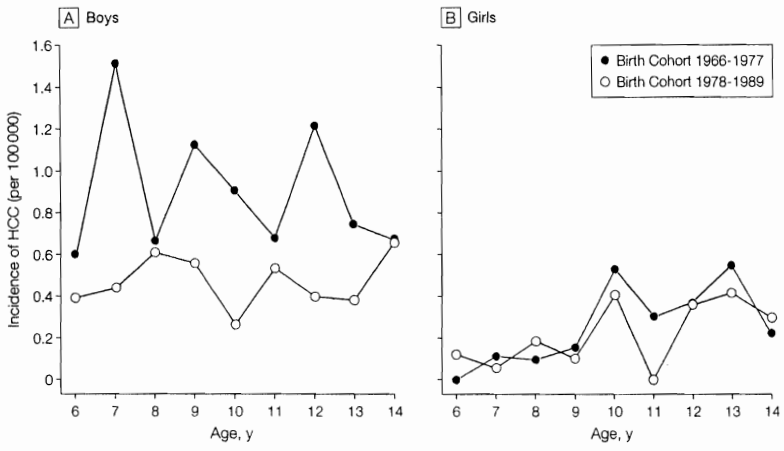
The relative risk (RR) of HCC in boys born between 1978 and 1984 declined significantly in comparison with those born before 1978 (RR, 0.83; $P=.02$); the trend of decrease in the RR of HCC was even more evident in those born after 1984 when compared with those born before 1978 (RR, 0.72; $P=.002$) (TABLE 2). However, the trend of decline in girls was not significant for the birth cohort born between 1978 and 1983 vs those born before 1978 (RR, 1.02; $P=.90$) or for those born after 1984 vs those born before 1978 (RR, 0.77; $P=.20$).

The age trend of HCC risk was significantly modified by sex. The risk of HCC in boys remained constant from age 6 to 14 years, while the risk of HCC in girls, though lower than in boys, increased significantly with age. In separate models, there was no significant age trend for boys (RR, 0.97; 95% CI, 0.92-1.03; $P=.33$), while the incidence of HCC in girls increased significantly by 1.15 times for each year increment of age (RR, 1.15; 95% CI, 1.04-1.28; $P=.007$). The age effect in boys and girls was the same before and after vaccination (FIGURE).

COMMENT

In the present study, we observed a predominance of HCC in boys both before and after the HBV vaccination pro-

Figure. Incidence of Hepatocellular Carcinoma (HCC) in Boys and Girls Aged 6 to 14 Years



A, The incidence of HCC in boys born after July 1978 was significantly lower than in those born before July 1978 ($P=.001$). The incidence of HCC in boys from 6 to 14 years did not change regardless of the birth year, suggesting that the age effect on the incidence of HCC was not prominent in boys. B, The incidence of HCC in girls aged 6 to 14 years increased with age, regardless of the birth year. The incidence of HCC in girls did not change in different birth cohorts.

gram. This predominance cannot be explained by the effect of sex hormones, as in adults. Tumor suppression gene regulation, the metabolism of carcinogens, or genetic alterations have been proposed to differ between men and women and need further study.[5]

This predominance decreased after the vaccination program because the incidence of HCC decreased significantly in boys but not in girls. Why the vaccination program seems to have had more of an effect on boys remains unclear. The low incidence of HCC in girls may render the statistical comparison of the incidences difficult. It is possible that HCC in girls is less intimately related to HBV infection than in boys, but seems unlikely given our previous observations[2] and evidence of HBV infection in girls with HCC born after implementation of the program (unpublished data by authors). The possibility that intrauterine infection with HBV, which would not be affected by vaccination, occurs more frequently in female infants also is unlikely, as there was no female predominance in infants who were seropositive for the hepatitis B surface antigen at birth.[12] Additionally, there was no difference in the vaccination coverage rate between male and female infants in Taiwan. (National Taiwan University Hospital's coverage rate is 100% for all mature neonates. The number of delivery of neonates is approximately 3000 per year. The national coverage rate for neonates was between 84% and 94% for 1986 to 1994 [M. H. Chang, unpublished data]). It also seems unlikely that case finding for such a serious disease would differ between boys and girls or change over time.

Seroepidemiologic studies in Taipei conducted in both 1984 and 1994 in children showed no or a slight predominance in boys in the incidence of HBV infection.[3,13] In contrast, the remarkable predominance of HCC in boys suggests that factor(s) in addition to chronic HBV infection may contribute to hepatocarcinogenesis in males, particularly the early occurrence in prepubertal males.

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